Bowel **A**nd **B**ladder function in **I**nfant **T**oilet **T**raining (**BABITT**)

- a randomized multicenter intervention study, to investigate the efficacy of assisted infant toilet training on the prevention of functional gastrointestinal and urinary tract disorders in Swedish children up to 4 years of age.

NCT04082689

October 25, 2021, protocol version 2.0

1. Title in English

Bowel **A**nd **B**ladder function in **I**nfant **T**oilet **T**raining (**BABITT**) – a randomized multicenter intervention study, to investigate the efficacy of assisted infant toilet training on the prevention of functional gastrointestinal and urinary tract disorders in Swedish children up to 4 years of age.

Title in Swedish

Tarm- och blåsfunktion hos barn som startar potträning under det första levnadsåret (**BABITT**) – en randomiserad interventionsstudie

2. Trial registration

ClinicalTrials.gov: NCT04082689
ClinicalTrials.gov protocol ID: BABITT-01

Primary registry and trial identification number	ClinicalTrials.gov: NCT04082689
Date of registration in primary registry	June 12, 2019
Secondary identification numbers	Not applicable
Sources of monetary or material support	Region Dalarna, Center for Clinical Research Dalarna, Regional Research Council of Uppsala- Örebro, The Mayflower Foundation, The Samaritan Foundation, The Swedish Enuresis Academy
Primary sponsor	Region Dalarna
Secondary sponsor(s)	Not applicable
Contact for public enquiries	Isabell Boväng Östman, Address: Nissers väg 3, S-791 82 Falun, Sweden Telephone: +46 (0)702-83 38 35 Email: isabell.bovangostman@regiondalarna.se
Contact for scientific queries	Barbro Hedin Skogman, PI Address: Nissers väg 3, S-791 82 Falun, Sweden Telephone: +46 (0)703-09 11 01 Email: barbro.hedinskogman@regiondalarna.se
Public title	Tarm- och blåsfunktion hos barn som pottränas under det första levnadsåret
Scientific title	Tarm- och blåsfunktion hos barn som pottränas under det första levnadsåret (**BABITT**) – en randomiserad interventionsstudie
Countries of recruitment	Sweden
Health conditions or problems studied	Functional constipation in children, infant colic, infant dyschezia, bladder dysfunction, process of infant toilet training, infant-to-mother attachment, parental stress
Intervention(s)	Intervention 1 (**Group A**): Infant toilet training starting at inclusion to the study (but no later than the age of 3 months). To be active in assisted infant toilet training is defined by the making of at least one attempt a day (without the requirement of a successful outcome) on at least 5 out of 7 days per week. Intervention 2 (**Group B**):

	Infant toilet training starting at 9-11 months of age. To be active in assisted infant toilet training is defined by the making of at least one attempt a day (without the requirement of a successful outcome) on at least 5 out of 7 days per week.
Key inclusion and exclusion criteria	Ages eligible for study: Infants younger than 2 months, 1 week and 6 days at inclusion. Sexes eligible for study: Female or male. Inclusion criteria: • Full-term infant (born at gestational week 37+0 to 41+6) Exclusion criteria: • Infants with malformations or disorders that may affect the gastrointestinal or urinary tract in any relevant way • Infants born small for gestational age (SGA), <-2 SD • Parents with insufficient understanding of the Swedish language • Infants older than 2 months, 1 week and 6 days at inclusion
Study type	Interventional Allocation: randomized Masking: specialized staff performing objective measurements Intervention model: parallel assignment Purpose: prevention
Date of first enrollment	April 18, 2019 (an internal pilot study)
Target sample size	Total of 268 infants (134 in each intervention group)
Recruitment status	Recruiting
Primary outcomes	• Prevalence of functional constipation (defined according to ROME IV criteria) up to 9 months of age • Prevalence of infant dyschezia (defined according to ROME IV criteria) up to 9 months of age • Prevalence of infant colic (defined according to ROME IV criteria) up to 5 months of age
Key secondary outcomes	• Prevalence of functional constipation (defined according to ROME IV criteria) up to 4 years of age • Prevalence of gastrointestinal symptoms measured with Pediatric Quality of Life Inventory Gastrointestinal Symptoms Module, (**PedsQLGastro**) at 4 years of age • Prevalence of stool toileting refusal up to 4 years of age • Prevalence of bladder dysfunction and/or urinary tract infections up to 4 years of age • Infant-to-mother attachment measured with Maternal Postnatal Attachment Scale (**MPAS**) up to 9 months of age • Parental stress measured with Swedish Parenthood Stress Questionnaire (**SPSQ**) up to 2.5 years of age • Experiences of the toilet training process up to 2.5 years of age

3. Protocol version

Revision chronology:

Protocol version 1.0, June 4, 2020, Original

Protocol version 2.0, May 27, 2021: Amendment 1, Authors: *TN, BHS*

Primary reason for amendment: changes in description of intervention, section 11, adjustments made due to the corona pandemic: introductory meeting was held as an online video meeting, the educational parental forum was cancelled, parents receive additional information about obtaining daytime dryness sent as an email. Additional changes (these changes themselves would not justify a protocol amendment): update of sponsor contact information in section 5b; clarifying section about internal pilot phase in section 8; clarifying sentence about day care services in section 9.

Protocol version 2.0, October 25, 2021: Amendment 2, Authors: *TN, BHS*

Primary reason for amendment: further correction in section 8, date for first recruitment of study participant in the internal pilot phase was corrected to April 18, 2019. Appendix in Swedish language (consent and participant information forms) was deleted from the study protocol upon request.

4. Funding

Region Dalarna, Center for Clinical Research Dalarna, Regional Research Council of Uppsala- Örebro, The Majblomman Foundation, The Samaritan Foundation, The Swedish Enuresis Academy.

5. Roles and responsibilities

Research group:

Barbro Hedin Skogman, *BHS*, senior consultant at the Department of Pediatrics, Falun Hospital, Associate professor at Örebro University and post-doctoral researcher at the Center for Clinical Research (CKF) Dalarna. Main supervisor to Anna Leijon and Terese Nilsson.

Anna Leijon, *AL*, resident in family medicine Dalarna, PhD student at Örebro University and at the Center for Clinical Research (CKF) Dalarna.

Terese Nilsson, *TN*, resident in family medicine Dalarna, PhD student at Örebro University and at the Center for Clinical Research (CKF) Dalarna.

Ulla Sillén, *US*, senior consultant and professor emerita, Department for Pediatric surgery, University of Gothenburg. Co-supervisor to Anna Leijon and Terese Nilsson.

Anna-Lena Hellström, *ALH*, urotherapist and professor emerita, Institute of Health and Care Sciences, University of Gothenburg. Co-supervisor to Anna Leijon and Terese Nilsson.

Cathrine Gatzinsky, *CG*, consultant and PhD student, Department for Pediatric surgery, University of Gothenburg. Responsible for the cohort of children constituting the reference material (**Group C**).

Elisabet Gustavsson, *EG*, pediatric surgeon and PhD at the Children's Hospital, Uppsala and at Uppsala University. Researcher competent in the field of bowel dysfunction and gastrointestinal disorders.

Malin Borgström, *MB*, pediatric nurse and urotherapist at the Department of Pediatrics, Falun and PhD student (project on enuresis) at Uppsala University and at the Center for Clinical Research (CKF) Dalarna. Specialized pediatric nurse performing ultrasound measurements of rectum in the **BABITT**-study.

Co-workers:

Eva Eriksson, *EE*, nurse at the Department of Pediatrics, Falun. Study coordinator.

Lilian Göras, *LG*, pediatric assistant nurse at the Department of Pediatrics, Falun. Specialized co-worker performing ultrasound measurements of rectum in the **BABITT**-study.

Aldina Pivodic, *AP***,** medical statistician at Statistical consulting group, Gothenburg.

5a. Authors' contributions:

BHS, *AL*, *TN, ALH* and *US* initiated the study and decided on the study design. *BHS*, *AL* and *TN* drafted the study protocol*. ALH, US* and *EG* revised the study protocol*.* All authors contributed to refinement of the study protocol and approved the final protocol version 1.0.

5b. Sponsor contact information

Trial Sponsor: Region Dalarna
Sponsor's reference: organization number: VAT SE 232100-0180
Contact name: Björn Äng, research manager
Address: Region Dalarna, Vasagatan 27, S-791 37 Falun, Sweden
Telephone: +46 (0)23-490000
Email: bjorn.ang@regiondalarna.se

5c. Sponsor and funder

Sponsor and funders have not been involved in the design of the study, and will not have any role during its execution, analyses, interpretation of the data or decision to submit results to scientific journals.

5d. Committees

Not applicable.

6. Introduction

6a. Background and rationale

In the last decades the average age for toilet training has increased in the western world (1). In the 1960's the vast majority of Swedish children were regularly using the potty by their first birthday (2). In contrast, being in diapers at the age of three is not unusual today (3). It is suggested that the postponed initiation of toilet training is a contributing factor to problems related to bowel and bladder control (4-9).

In Vietnam, toilet training starts in early infancy by tradition. By the age of nine months, the majority of children achieve parent-assisted dryness (10). In the western world this technique for early toilet training has received attention, by the term "Elimination Communication" or "Infant Toilet Training". As the caregiver responds to the elimination signals and routines of the child by taking it to a designated place to relive itself rather than in a diaper, the baby's cues and ability to convey elimination needs are gradually enhanced. Through this responsive interaction, a two-way communication pathway opens between the caregiver and the child (11). In infant toilet training, the baby is held in a squat position over some sort of receptacle (e.g. potty or basin). Studies in adults have shown that a squat position straightens the rectal angle, thus facilitating fecal evacuation (12).

The Swedish National Guide to Child Health Care is web-based decision support, providing evidence-based guidelines for Swedish Child Health Care (CHC) centers. In 2015, a new recommendation was

published, stating that initiation of toilet training should be encouraged at the 10-month visit and preferably before the child can walk (13).

Infant colic is characterized by inconsolable crying or fussing without obvious cause in infants under the age of five months. A recent systematic review found that the overall prevalence of infant colic ranged from 17-25% during the first 6 weeks of life (14). Infant colic is a functional disorder that often causes great stress for the family while it is ongoing, despite its benign and self-limited character. The cause of infant colic is unknown (15).

Infant dyschezia is a functional condition in children <9 months of age defined by at least 10 minutes of straining and crying before successful or unsuccessful passage of soft stools (16). Prevalence varies from 0.9-3.9% in children <9 months. The cause is considered to be failure to coordinate increased intra-abdominal pressure with relaxation of the pelvic floor muscles (16).

In the newborn, incomplete voiding and residual urine is normal. This is caused by dyscoordination between the expelling bladder muscle and the closing sphincter. As shown by a study on Vietnamese and Swedish children (17), coordination develops in association with toilet training and not through passive maturation, as previously prevailing opinion has suggested. Symptoms of bladder dysfunction are common in school-age children and primarily present as urgency and incontinence (18-20). Constipation affects bladder function. This is illustrated by the fact that symptoms of bladder dysfunction as well as recurrent urinary tract infections generally disappear with the treatment of concomitant constipation (21).

The prevalence of constipation, as presented in international studies, is very variable (0.7–30%), possibly due to the multifactorial nature of the condition, but also due to the lack of uniform definitions (22). According to preliminary results from an ongoing Swedish study, the prevalence of constipation is estimated to 10-15% during the first year of life (personal communication). In most cases of children with constipation (> 90%), the condition is defined as functional constipation, i.e. no organic cause is found (22). Despite good treatment options, it has been shown that quality of life in constipated children is significantly decreased compared to children without constipation (23, 24). Furthermore, children often suffer relapses during childhood and up to a third still experience symptoms of constipation in adulthood (25-27).

The effect of infant toilet training on functional gastrointestinal disorders (functional constipation, infant dyschezia and infant colic) or urinary tract disorders (bladder dysfunction and urinary tract infection) in children, has not previously been studied. If infant toilet training can prevent functional gastrointestinal or urinary tract disorders, significant health benefits are to be expected due to reduced suffering for the children and their families, as well as a more effective use of healthcare resources. Learning more on when and how it is beneficial to introduce the potty in a modern family setting, in a Swedish cultural context, is crucial to elaborate upon appropriate guidelines on toilet training.

The results of the **BABITT**-study could lay the foundation for new evidence-based recommendations on toilet training carried out by the Swedish Child Health Care centers. Moreover, substantial international interest is to be expected, as results could be implemented in other healthcare systems.

6b. Choice of comparators

The Swedish National Guide to Child Health Care stated in 2015 that the CHC should encourage initiation of toilet training on the 10-month visit (13). Therefore, it was unethical to recruit parents who would not receive any advice or intervention on toilet training in children older than 9-11

months. Consequently, in the **BABITT**-study, the control group consists of children who have ***not*** yet been introduced to toilet training (**Group B**, described below). See Figure 1.

Furthermore, two reference materials, outside the **BABITT**-study, are chosen as comparators, consisting of children, who did ***not*** start toilet training during the first year of life (**Group C** and **Group D**, described below). See Figure 1.

Group C comprises 110 healthy children in an ongoing longitudinal study in Gothenburg, regarding bowel and micturition habits in healthy children (*GC*, personal communication). Infants were recruited from 2014-2019. Children in Group C have ***not*** been introduced to toilet training during the first year of life and are thus suitable reference material for the **BABITT**-study. The questionnaires used in Group C are congruent with those of the **BABITT**-study.

Group D will consist of 4-year-old children in a cross-sectional study called **BABIS-4** (**B**owel and **B**ladder function **I**n **S**wedish **4**-year olds). The **BABIS-4** study is designed and planned by the research group (*AL, TN, BHS, ALH, US*) and will recruit 4 year old children during 2020-2021, at the same CHC units as those participating in the **BABITT**-study in Dalarna, Sweden. In a randomly selected 10% of the study participants in **Group D**, the same specialized staff as in the **BABITT**-study will perform ultrasound measurements of the rectum. See separate study protocol. The questionnaire answered by **Group D** is congruent with the questionnaire at 4 years of age in the **BABITT**-study.

B A B I T T reference groups and measuring points

Age	2 w	1 mo	2 mos	3 mos	6 mos	9 mos	1 yr	1,5 yrs	2 yrs	2,5 yrs	4 yrs
Group A Group B			X	X	X	X rectal ultrasound	X	X	X	X	X rectal ultrasound
Group C	X		X rectal ultrasound		X rectal ultrasound		X rectal ultrasoun	X		X	X rectal ultrasound
Group D											X rectal ultrasound

Figure 1. Time schedule for measuring points for questionnaires (web surveys) (**X**) and rectal ultrasound for the **BABITT**-study (**Group A** and **Group B**) and reference groups (**Group C** and **Group D**).

7. Objectives

The overall objective is to obtain knowledge on whether assisted infant toilet training, initiated during the first year of life, affects the prevalence of functional gastrointestinal or urinary tract disorders up to 4 years of age.

Research hypothesis

Assisted infant toilet training initiated at 0-3 months of age reduces the prevalence of functional gastrointestinal disorders (constipation, infant dyschezia and infant colic) up to 9 months of age.

Assisted infant toilet training initiated during the first year of life reduces the prevalence of functional gastrointestinal and urinary tract disorders up to 4 years of age.

Primary research questions

- Is the prevalence of functional gastrointestinal disorders (constipation, infant dyschezia and infant colic) reduced in children introduced to toilet training at 0-3 months of age (**Group A**), as compared to children who are ***not*** introduced to infant toilet training (**Group B**), up to 9 months of age?

Secondary research questions

- Is the prevalence of functional gastrointestinal disorders (constipation, gastrointestinal symptoms and/or stool toileting refusal) reduced in children introduced to toilet training at 0-3 months of age (**Group A**), compared to children introduced to toilet training at 9-11 months of age (**Group B**), when followed up until 4 years of age?

- Is the prevalence of urinary tract disorders (bladder dysfunction and/or urinary tract infections) reduced in children introduced to toilet training at 0-3 months of age (**Group A**), compared to children introduced to toilet training at 9-11 months of age (**Group B**), when followed up until 4 years of age?

- Is the prevalence of functional gastrointestinal and urinary tract disorders reduced in children introduced to toilet training during the first year of life (**Group A** and **Group B**), compared to children ***not*** introduced to toilet training during the first year of life (reference **Group C** and **Group D,** described above), when followed up until 4 years of age?

- Does infant-to-mother attachment differ in families when initiating infant toilet training at 0-3 months of age (**Group A**), compared to families ***not*** practicing infant toilet training (**Group B**), up to 9 months of age?

- Does parental stress differ in families when initiating infant toilet training at 0-3 months of age (**Group A**), compared to families ***not*** practicing infant toilet training (**Group B**), up to 2.5 years of age?

- Are there differences regarding the toilet training process in children introduced to toilet training at age 0-3 months (**Group A**), compared to children introduced to toilet training at age 9-11 months (**Group B**), when followed up until 2.5 years of age?

- What are the overall parental experiences of infant toilet training initiated during the first year of life (**Group A** and **Group B**), up until 2.5 years of age?

8. Study design

The **BABITT**-study is designed as a randomized, controlled, investigator blinded, two-armed intervention, multicenter study with follow-up until 4 years of age. Randomization will be performed as block randomization with a 1:1 allocation.

The study protocol is written in the form of the SPIRIT 2013 Statement Explanation and Elaboration paper, in order to be able to be published according to the SPIRIT 2013 checklist (28).

Internal pilot phase

An internal pilot phase of the full intervention was conducted during 12 months at one CHC center. The internal pilot phase started recruitment in April 2019. The aim was to evaluate study participant eligibility, recruitment rate, withdrawal rate and reason for withdrawal, completion of web based questionnaires and intervention adherence and acceptablity. Also to gain knowledge of the CHC nurses acceptability of the intervention and recruitment, experienced work load and logistics of the study. After evaluation, minor corrections were made to ensure data collection and to enhance study logistics. The study participants in the internal pilot phase (n=22) therefor are accepted to continue as included participants in the BABITT-study and will be retained in the full study analysis.

Recruitment is anticipated to continue throughout 2021.

Prior to drafting the study design, qualitative work with focus group interviews with CHC nurses and parents was performed by *AL* and *TN* (unpublished data) in order to better understand the study setting(29, 30).

The questionnaries used in the BABITT-study were validated by a CVI process, further description of the process in section 18.

Report of results from the study will follow the CONSORT statement (31).

9. Study setting

The **BABITT**-study is conducted at several CHC centers in an urban-rural setting in central Region Dalarna, Sweden. The CHC centers are chosen primarily geographically for operational purposes. The full list of CHC centers is available at ClinicalTrials.gov.

The Swedish CHC is nurse-led, free of charge, available to almost everyone (99%) and focuses on preventive care (32).

The social insurance system in Sweden provides a parental leave compensation for 480 days. Three months are exclusive to each parent; the rest can be divided as the family decides. Day care services is available from 1 year of age and is available for all families since the cost is highly subsidized. Of all

children in Sweden, 80 % are attending day care by 2 years of age (32). At the time of the start of the study, the Swedish day care services do not have any general recommendations on toilet training or support in regular toilet habits.

At the Pediatric Department at Falun Hospital, specialized staff (*MB* and *LG*) will perform the ultrasound measurements of rectal diameter.

10. Eligibility criteria

Inclusion Criteria

- Full-term infant (born at gestational week 37+0 to 41+6)

Exclusion Criteria

- Infants with malformations or disorders that may affect the gastrointestinal or urinary tract in any relevant way
- Infants born small for gestational age (SGA), <-2 SD
- Parents with insufficient understanding of the Swedish language
- Infants older than 2 months, 1 week and 6 days at inclusion

11. Description of intervention

The intervention consists of parents practicing infant toilet training with their child.

Preceding the study start, the CHC nurses are given two 60-minute lectures (by *AL* and *TN*) on infant toilet training techniques and the **BABITT**-study structure and logistics. They receive a book ("Bebis på pottan") (33) containing more elaborate descriptions of techniques and parental experiences of infant toilet training, as well as a brief summary of it produced by the study researchers (*AL* and *TN*).

The CHC nurses set up an introductory meeting for children eligible for the study. Due to the corona pandemic the introductory meeting was an online video meeting. At this meeting the parents are given information on the study by *AL* or *TN*. After receiving informed consent from both parents, group allocation is determined by randomization.

Parents allocated to **Group A** are prompted to initiate toilet training as soon as possible, but no later than at 3 months of age. After the introductory meeting they receive a potty, oral instructions in how to perform infant toilet training, a book on the topic ("Bebis på pottan") (33) as well as a brief summary of the book produced by researchers (*AL* and *TN*).

Parents allocated to **Group B** are instructed to start toilet training by 9 months of age, but no later than at 11 months of age. **Group B** will receive the information and material described above, at the ultrasound appointment at the Pediatric Department at 9 months of age. All parents were offered a

toilet seat at the ultrasound appointment, or on beforehand, if parents allocated to group A contacted the study researchers or CHC nurse.

For further guidance, an educational parental forum was held during 2019. Because of the corona-pandemic, the educational parental forum was cancelled. Parents were instead encouraged to contact their CHC nurse or the study researchers (*AL and TN*) if further guidance is needed.

In the event of infant colic, a behavioral diary is filled in by the parents (same instructions given to both groups at inclusion). General recommendations are given by the CHC nurse, in accordance with The Swedish National Guide to Child Health Care (34), to both groups. The general recommendations include routine examination by a family physician to rule out organic cause, a test period of milk protein free diet (in infant formulas or in mothers' diet if breast-fed), testing probiotic containing Lactobacillus Reuteri and psychosocial support.

To ensure data collection, the study coordinator (*EE*) will telephone parents who stated in the web survey at 2 months of age that their child has periods of prolonged crying, fussing, or irritability without obvious cause for more than 60 minutes per day, and encourage them to fill in the behavioral diary. The study coordinator (*EE*) documents the parents' comments and experiences. Parents of infants with colic allocated to **Group A** will be encouraged to continue and possibly intensify infant toilet training, whereas infants allocated to **Group B** will be given care as usual, but no instructions in infant toilet training.

Intervention-adherence

In each web survey the parents are asked to what extent they perform infant toilet training. Parents of children allocated to group B are asked in the web survey at 2, 3, 6 and 9 months of age, if they are obeying the group allocation and not undertaking infant toilet training.

To ensure adherence to the intervention, the study researchers (*AL* or *TN*) will contact parents of children allocated to group A, if they stated in the web survey at 2 months of age that they conduct infant toilet training less than 5 days per week. The parents are asked what obstacles they are facing and if they need support or more information. The parents were offered to obtain a toilet seat. If the child was recruited to the study less than two weeks before the parents answered the 2-month web survey, the study researchers (*AL* or *TN*) waits two weeks (but not beyond the child becoming 3 months old, before calling. The same procedure is done with parents of children allocated to group B, if they stated that they conduct infant toilet training less than 5 days per week at the 12-month web survey.

Swedish day care services do not have any recommendations on toilet training. The clinical experience of parents performing infant toilet training is that day care services seldom offer support in regular toilet habits. This can result in relapse in dryness and a need to use diaper at the day care services. The study researchers (*AL* and *TN*) therefor held a lecture on infant toilet training, the **BABITT**-study structure and the current guidelines for Swedish CHC centers to principals of affected day care services. The lecture was filmed and distributed to staff working at day care services.

At 9 months of age parents will be encouraged to give a written summary of the **BABITT**-study structure and the current Swedish guidelines for toilet training to the day care service their child will attend to.

At 18 months parents receive an encouraging additional information (sent as an email) prompting the parents to plan and start the process of daytime dryness. It contained the information that it is best to achieve daytime dryness before the age of 2,5 years, to prevent problems with bowel and bladder.

12. Outcomes

Primary outcomes

- Prevalence of functional constipation (defined according to ROME IV criteria) up to 9 months of age
- Prevalence of infant dyschezia (defined according to ROME IV criteria) up to 9 months of age
- Prevalence of infant colic (defined according to ROME IV criteria) up to 5 months of age

Secondary outcomes

- Prevalence of functional constipation (defined according to ROME IV criteria) up to 4 years of age
- Prevalence of gastrointestinal symptoms measured with Pediatric Quality of Life Inventory Gastrointestinal Symptoms Module (**PedsQLGastro**) at 4 years of age
- Prevalence of stool toileting refusal up to 4 years of age
- Prevalence of bladder dysfunction and/or urinary tract infections up to 4 years of age
- Infant-to-mother attachment measured with Maternal Postnatal Attachment Scale (**MPAS**) up to 9 months of age
- Parental stress measured with Swedish Parenthood Stress Questionnaire (**SPSQ**) up to 2.5 years of age
- Experiences of the toilet training process up to 2.5 years of age

Full list of outcome measures

1. Questionnaire (web survey) at 2, 3, 6, 9, 12, 18 months and at 2, 2.5 and 4 years, validated in pilot study by Content Validity index (**CVI**) (35)
    a. Functional constipation, infant dyschezia and infant colic, defined according to ROME IV criteria (16) (also journal review o/d)
    b. Abdominal pain (also journal review o/d)
    c. Stool toileting refusal (7)
    d. Bowel and bladder function defined according to ICCS (18)
    e. Urinary tract infection (also journal review o/d)
    f. Toilet training process
    g. Use of laxatives
    h. Breastfeeding and nutrition
    i. Social situation, age and level of education of parents, presence of siblings, family history of constipation and attendance at pre-school
    j. Intervention adherence

2. Validated rating scale (web survey)
    a. Infant-to-mother attachment, measured with Maternal Postnatal Attachment Scale (**MPAS**) (36) at 3 and 9 months of age

b. Parental stress, measured with Swedish Parenthood Stress Questionnaire (**SPSQ**) (37) at 3, 9 and 18 months and 2.5 years of age
c. Gastrointestinal symptoms, measured with Pediatric Quality of Life Inventory Gastrointestinal Symptoms Module (**PedsQLGastro**) (38), at 4 years of age

3. Observational lists (filled in by parents)
   a. Infant behavioral diary (16) (24 hour prospective registration) when infant colic is suspected

4. Investigations
   a. Rectal diameter determined by ultrasound measurement (39) at 9 months and 4 years

13. Participant timeline

Children must be included before reaching 2 months, 1 week and 6 days, but preferably as early as possible.

Web surveys are conducted at 2, 3, 6, 9, 12, 18 months and at 2, 2.5 and 4 years (see Figure 2). A 28-day window (defined as 14 days before and 14 days after the due date), is allowed for the 2, 3 and 6-month survey. At 9 months, a 44-day window is allowed (14 days before and 30 days after the due date) and at 12, 18 months and at 2 and 2.5 years a 60-day window is allowed (30 days before and 30 days after the due date). At 4 years of age a 120-day window will be allowed (30 days before and 90 days after the due date).

For the rectal ultrasound measurement at 9 months of age, a 60-day window will be desired (14 days before and 46 days after the due date). At 4 years of age, a 120-day window will be desired (30 days before and 90 days after the due date).

B A B I T T measuring points											
Age	**0 mo**	**1 mo**	**2 mos**	**3 mos**	**6 mos**	**9 mos**	**12 mos**	**18 mos**	**2 yrs**	**2,5 yrs**	**4 yrs**
	Enrolment in study										
Infant toilet training		**Group A** infant toilet training and parental forum*									
							Group B infant toilet training and parental forum*				
Validated Questionnaire (web survey)			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
External validated instruments (web survey)				**MPAS SPSQ**		**MPAS SPSQ**		**SPSQ**		**SPSQ**	**PedsQL**
Investigation						**Rectal ultrasound**					**Rectal ultrasound**
Infant behavioural diary (when applicable)	**(+)**	**(+)**	**(+)**	**(+)**							

Figure 2. Time schedule for measuring points for questionnaires (web surveys) (**X**) including Maternal Postnatal Attachment Scale (**MPAS**), Swedish Parenthood Stress Questionnaire (**SPSQ**), Pediatric Quality of Life Inventory Gastrointestinal Symptoms Module (**PedsQL**), rectal ultrasound and infant

behavioral diary (**+**) in the **BABITT**-study (**Group A** and **Group B**).
*participation in educational parental forum is offered.

14. Sample size

The sample size was calculated on the prevalence of functional gastrointestinal disorders (functional constipation, infant dyschezia or infant colic), at age 9 months. In the literature the prevalence of functional constipation varies between 0.7-30% (22), unpublished data from an ongoing Swedish cohort (**Group C**) indicate 7% prevalence at 1 year of age (*GC*, personal communication).

The prevalence of infant dyschezia varies between 0.9-3.2% (16). Unpublished data from **Group C** indicate a prevalence of 18% at 2 months of age and 4% at 6 months of age (*GC*, personal communication).

The prevalence of infant colic varies between 17-25% at 6 weeks of age (14).

We therefore argue that a total prevalence of these disorders could be set to 15% of the general population (congruent with **Group B)** and could be estimated to 4% of children who have been introduced to infant toilet training (congruent with **Group A**).

In order to find a statistically significant difference ($p<0.05$) between groups with an 80% power, 121 children are required in each study group. With an estimated 10% shortfall, 134 children will be included in each study group, which gives a total number of 268 children in the **BABITT**-study.

15. Recruitment

All new-borns registered at the participating CHC centers in Region Dalarna are eligible for the study, up to 2 months, 1 week and 6 days of age. Written and oral information about the study is given by midwives before childbirth (at the 35 gestational week visit) and at the first visits after childbirth by the CHC nurses. For recruitment purposes, posters with written information of the study are available at the CHC centers. The family physicians working at the CHC centers are encouraged to address the parents regarding the study at the routine medical examination at one month of age.

16. Allocation

Participants are randomly assigned to either **Group A** or **Group B** with a 1:1 allocation. The randomization is performed by the researchers responsible for inclusion (*AL* and *TN*), by using a computer program designed by MediCaseAB (40). The randomization is stratified by the gender of the child using permuted blocks. The block size will not be disclosed, to ensure concealment. Allocation concealment will be ensured since randomization is only possible after the researchers (*AL* and *TN*) have completed all the baseline data.

17. Blinding

Due to the nature of the intervention, parents are informed by the researchers (*AL* and *TN*) which group they are allocated to. Their CHC nurse is informed when the child enters the study and the group allocation.

The parents and the CHC nurses are informed that the study involves testing two different forms of infant toilet training, and that both are considered equal options. **Group A** reflects how infant toilet training is conducted in Vietnam (10) and **Group B** reflects how we introduced the potty in Sweden in the 60´s (2). **Group B** is also in line with the current recommendations provided by The Swedish National Guide to Child Health Care (13).

The group allocation (**Group A** or **Group B**) of the participating children will be masked to the specialized staff (*MB* and *LG*) performing the ultrasound measurement of rectal diameter at 9 months and 4 years of age. The parents are asked not to reveal their group allocation to the specialized staff (*MB* and *LG*) performing the rectal ultrasound measurement.

When the study is closed, all statistical analyses will be performed with the statistician masked to group allocation.

18. Data collection methods

18a. Data collection and description of instruments

At inclusion the parents are asked who of the two caregivers will be on parental leave for the first months with the child. The parent on parental leave first will be asked to fill in all the web surveys in the **BABITT**-study, and therefore the web survey is sent to that parent's email address. This will enable comparisons over time of each parent's experience regarding parenthood stress (**SPSQ**) (37), and mother-to-infant attachment (**MPAS**) (36). Using electronic web surveys filled in directly by the parent on their own smart phone, tabloid or computer, ensures data accuracy, user acceptability and timeliness of data receipt.

All items in the questionnaires (web surveys) were validated in the internal pilot phase as per the Content Validity Index (**CVI**) (35). In this process, a panel of eight experts have individually scrutinized each item in the questionnaires. This panel consisted of two M.D.s with pediatric competence, two researchers with relevant scientific competence and four parents with personal experience of infant toilet training. The different items receive individual comments and scores on relevance and simplicity, from which a total score is calculated. The comments and scores were then analyzed by the researchers (*AL*, *TN* and *BHS*) following a revision of the items. After a second round of comments and scores from the expert panel, the items got through a final revision by the researchers and the total score of the second round can be compared to the score of the first round.

The study coordinator (*EE*) is easily alerted by the electronic clinical research form (eCRF) when the due date to answer the web survey is passed. The study coordinator (*EE*) then contacts the parent by text message or telephone call to remind them to fill in the web survey before the end of the window for the survey is passed. If the parent isn´t able to answer the web survey due to technical problems, the study coordinator (*EE*) can read the questions and directly fill in the eCRF accordingly.

Functional constipation is defined in accordance with ROME IV (16). At least 2 of the following criteria are required during a one-month period:

- ≤2 defecations per week
- History of excessive stool retention
- History of painful or hard bowel movements
- History of large-diameter stools
- Presence of a large fecal mass in the rectum

In toilet-trained children the following additional criteria may be used:

- Stool incontinence at least once a week
- History of large-diameter stools that may obstruct the toilet

Infant dyschezia is defined in accordance with ROME IV criteria (16):

- Healthy infant ≤9 months of age at the onset and cessation of symptoms
- At least 10 minutes straining and crying before successful or unsuccessful passage of soft stools

Infant colic is defined in accordance with ROME IV (16). All of the following criteria are required:

- Healthy infant ≤5 months of age at the onset and cessation of symptoms
- Recurrent periods of prolonged crying, fussing, or irritability without obvious cause which cannot be prevented or resolved by caregivers
- No evidence of infant failure to thrive, fever, or illness
- Crying or fussing ≥3 hours during at least 3 days for a period of 7 days
- 24-hour prospective behavioral diary documenting ≥3 hours crying/fussing. Since there is no behavioral diary recommended by the ROME foundation, we have modified the infant behavioral diary used in a Swedish infant colic thesis (41).

Gastrointestinal symptoms, are measured with a Pediatric Quality of Life Inventory Gastrointestinal Symptoms Module (**PedsQLGastro**) (38) at 4 years of age. **PedsQLGastro** contains 58 items. The items are reverse-scored and linearly transformed to a 0-100 scale (0=100, 1=75, 2=50, 3=25, 4=0), so that lower scores demonstrate more GI symptoms, and hence, lower GI-specific health-related quality of life. The scale scores are computed as the sum of the items divided by the number of items answered.

Stool toileting refusal (STR) is defined by children who urinate in the potty/toilet but refuse to have a bowel evacuation there, for more than one month (7).

Rectal diameter will be measured with ultrasound (39) according to a method manual from the University of Gothenburg (*GC*, personal communication). An inter-rater agreement analysis will be performed on measurement results from the specialized staff (*MB* and *LG*) of the **BABITT**-study.

Bladder dysfunction is defined according to ICCS terminology (18):

- Urinary incontinence
- Enuresis
- Nocturia
- Voiding frequency ≤3 or ≥8 per day
- Urgency

Urinary tract infection is defined by the diagnoses N.30.0 (acute cystitis) and N30.9 (cystitis UNS) also N10.9 (acute tubulointerstitial nephritis).

Infant-to-mother attachment, is measured with Maternal Postnatal Attachment Scale (**MPAS**) (36) at 3 and 9 months of age. **MPAS** is measured by 19 issues. Questions are scored 1-5. Total score is calculated by adding scores on all issues. Scale range for total score is 19-95. A high score indicates higher mother-to-infant attachment.

Parental stress, is measured with Swedish Parenthood Stress Questionnaire (**SPSQ**) (37) at 3, 9 and 18 months and 2.5 years of age. **SPSQ** contains 34 issues each scoring 1-5. Total score is calculated as an average on answers (1-5) on all issues. Scale range for total score is 34-170. A high score indicates higher parental stress.

To obtain the complete questionnaires of the **BABITT**-study, please contact study researchers (*BHS*, *AL* or *TN)*.

18b. Retention of participants

Regardless of adherence, all participants will be included in an intention to treat analysis. Parents are encouraged to leave comments in a free text section in the web survey, in case of non-adherence to the intervention.

To ensure complete follow up, symbolic gifts will be given after the appointment for the rectal diameter measurements at the Pediatric Department. If the parents cannot attend, they are still encouraged to continue to fill in the web surveys.

Participants may withdraw from the study for any reason at any time. They are asked (but not obliged) to state the reason for withdrawing (according to GCP standards) in a form. It is clearly stated that withdrawal will not affect the future care given by the CHC centers. Participants may also be withdrawn if the study sponsor or government or regulatory authorities terminate the study prior to its planned end date.

19. Data management

All information collected in the **BABITT**-study will be electronically entered into the eCRF provided by MediCaseAB (40) and then securely stored in a database located in Sweden. Only the study researchers (*AL*, *TN* and *BHS*) and the study coordinator (*EE*) have a personal login to assess the eCRF. The personal information and contact information of the participants is not accessible assessable to MediCaseAB. Demographic data at inclusion in the study is entered electronically into the eCRF by the study researchers (*AL* and *TN*) and the parents fill in the web surveys electronically. The clinical research form (CRF) used during the measurement of the rectal diameter is entered in the eCRF by the study researchers (*AL* and *TN*) consecutively. At inclusion, study participants are given a specific study ID that is used on the paper CRF and in the behavioral diaries. Behavioral diaries are given to the CHC nurse who collects them in the clinic folder, and they are then consecutively entered in the eCRF by study researchers (AL and TN). Participant coded files will be stored in a secure manner at CHC centers, at the Department of Pediatrics at Falun Hospital and eventually all coded data will be stored at the Clinical Research Center Dalarna, Region Dalarna, Falun. Original data will be kept 10 years after the last publication.

In the eCRF there are range checks for data values when appropriate. Written documentation of all changes in the eCRF is available via electronic logs and audit trails.

All data will be coded under data processing and publication of results. The code key will be destroyed when no longer needed or 10 years after the last publication.

20. Statistical methods

The results will be analyzed in accordance with intention-to-treat. **Group A** will be compared with the control (**Group B**) for all primary analysis. For comparison of dichotomous variables between the groups, the Chi-2 or Fisher's extract test will be used. For continuous variables the Mann-Whitney U-test will be used for comparison between groups. For correlation and agreement between scales, Pearson's correlation test or Cohen's kappa will be used when appropriate. Subsequently logistic regression analysis will be used to evaluate outcome measures in relation to baseline data. For all tests, we will use 2-sided p-values with alpha ≤0.05 level of significance.

Further calculations will be made in accordance with statistical consultants in order to correctly compare **Group A**, **Group B** and reference materials **Group C** and **Group D**.

Quantitative longitudinal data will be analyzed statistically in conjunction with qualitative data (mixed method) from the questionnaires. Data will be analyzed according to the method described by Malterud (42). By this procedure, transcribed text from the comment sections is read in order to find overarching themes. Thereafter, meaningful elements are identified and extracted (de-contextualization), out of which condensed meaningful elements are created and grouped. The proceeding step is to re-formulate the content in summarized descriptions (re-contextualization). To assure preserved congruence, the text is compared to raw data. Finally, the result is validated by separate analysis by the other researcher (*AL* or *TN*).

A professional academic statistician will be blinded to study groups when conducting all statistical analyses.

21. Data monitoring

Since the **BABITT**-study is not a pharmacological trial, monitoring is not considered applicable. This is furthered supported by the fact that the group allocation is not blinded to the parents and the web surveys are filled in by the parents. The intervention is easy to perform and is not expected to do harm. No interim analysis will be performed.

22. Harms

Infant toilet training is widely spread over the world. In some cultures, it is part of the cultural heritage. In the western world, information is easily assessable on the internet. Reporting adverse effects by the CHC nurses over the long follow-up period was not needed for medical reasons, not possible due to the workload of CHC nurses and not suggested by the Ethical Review Board in

Uppsala. In the web surveys there are free text areas were the parents can report positive and negative experiences regarding infant toilet training.

23. Auditing

Not applicable.

24. Research ethics approval

The Ethical Review Board in Uppsala, Sweden, has reviewed and approved the study protocol, the scientific content and compliance with applicable research and human subject regulations. The application was approved 2018-11-14 (Dnr 2018 / 388) with a minor revision 2019-04-03 (Dnr 2019-01668).

25. Protocol amendments

Modifications to the study protocol that may impact on the conduct of the study, including changes of study objectives, study design, patient population, sample sizes or significant administrative aspects, will be added as a formal amendment to the protocol. Amendments will be agreed by the research group and approved by the Swedish Ethical Review Board in Sweden prior to implementation. Administrative changes of the protocol with minor corrections and/or clarifications that have no effect on the way the study is to be conducted will be agreed upon by the research group, and will be documented in a memorandum.

26. Consent

The CHC nurses give verbal information on the study and provide written information about the study. The written information is designed and approved according to the Swedish Ethical Review Board. If the parents are interested, an introductory meeting regarding the study is set between the parents and the study researchers (*AL* or *TN*). At the meeting, the parents get verbal informed about the study in a standardized manner and they are encouraged to ask questions. At the meeting, they are informed that participation is voluntary. If the parents agree to participate, AL or TN will obtain written informed consent from both parents.

27. Confidentiality

If parents are interested in the study the CHC nurses book a meeting in the electronic patient journal system used at the CHC centers. *AL* and *TN* have access to the journal system through personal login and can then contact the parents.

All information collected in the **BABITT**-study will be electronically entered into the eCRF provided by MediCaseAB (40), and then securely stored in a database located in Sweden. Only the study researchers (*AL*, *TN* and *BHS*) and the study coordinator (*EE*) have a personal login to assess the eCRF.

The personal information and contact information of the participants is not accessible to MediCaseAB.

At inclusion, study participants are given a specific study ID that is used on study forms to maintain confidentiality.

Participant coded forms will be stored in a secure manner at CHC centers, at the Department of Pediatrics at Falun Hospital and eventually all coded data will be stored at the Clinical Research Center Dalarna in Falun. Original data will be kept 10 years after the last publication from the study.

All data will be coded under data processing and publication of results. The code key will be destroyed when no longer needed or 10 years after the last publication.

28. Declaration of interests

The authors declare no competing interests.

29. Access to data

Only study researchers (*BHS*, *AL* and *TN*) will have full access to data. To ensure confidentiality only coded data will be accessible to the rest of the research group or the statistical co-worker. According to Swedish law and GDPR restrictions, a contract will be signed before access to any coded data is permitted.

30. Ancillary and post-trial care

All participants are insured according to national assurance of patients. Economical compensation for participation is not offered. Symbolic gifts will be offered during the study to enhance study participation. Public transportation is free of charge when going to the appointment at hospital, according to national standards. All medical care is free of charge up to 18 years of age in Sweden (32).

31. Dissemination policy

The **BABITT**-study and the cross-sectional study of 4 year-olds in Dalarna, **BABIS-4** (**Group D**) will form the basis for two PhD theses (by *AL* and *TN*). The results of the study are planned to be reported in appropriate international medical journals regardless of the magnitude or direction of effect. Every attempt will be made to reduce the time interval between the completion of data collection and the release of the study results. The study results will also be released to participating CHC centers and the general medical community.

Professional medical writers will not be used.

The full study protocol of the **BABITT**-study is published at ClinicalTrials.gov.

32. Informed consent materials

Consent and participant information forms are approved by the Swedish Ethical Review Board. See Appendix 1 (in Swedish).

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